REMARKS

This Amendment A is submitted responsive to the Office Action mailed November 19, 2007. Applicants respectfully request that these amendments and remarks be entered, and that the application so amended be reconsidered and allowed.

The Status of the Claims

Claims 1-31 were pending as of issuance of the Nov. 19th Office Action.

Claims 1-8, 10-12, 22-27, and 31 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Song et al., "Multislice Double Inversion Pulse Sequence for Efficient Black-Blood MRI", Magnetic Resonance in Medicine, vol. 47 pages 616-20 (2002) (hereinafter "Song").

Claims 9, 13-21, and 28-30 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Song in view of Van Zijl et al., "Quantitative assessment of blood flow, blood volume and blood oxygenation effects in functional magnetic resonance imaging", Nature Medicine vol. 4, pages 159-67 (1998) (hereinafter "Van Zijl").

Pages 5-6 of the Office Action also mention "Fritz '762" in reference to claim 9. This reference is not further identified, and the articulation of any rejection on the basis of this reference appears incomplete. Applicants do not address this portion of the Office Action, and ask for clarification in the forthcoming Office Action if any claim rejections based on "Fritz '762" is intended.

The claims are amended to remove reference numbers

The claims have been amended to remove the reference numbers. The use of reference characters in the claims is to be considered as having no effect on the scope of the claims. MPEP § 608.01(m). Accordingly, these amendments removing the reference numbers do not impact the scope of the claims.

Applicants request withdrawal of the rejections under § 102(b) based on Song

The Office Action identifies Song as a reference under § 102(b). Office Action at page 2. Song is indicated on its face as having published in 2002, and the Office Action also lists Song as having published in 2002.

The present application is a National Stage entry of PCT/US2003/26580 which has a priority date of August 27, 2002 through U.S. provisional application no. 60/406,040. The Office Action has not shown that Song published more than one year prior to the priority date of the present application. Accordingly, it is respectfully submitted that Song does not qualify as a reference under § 102(b), and Applicants request that the rejections under § 102(b) based on Song be withdrawn.

The Present Application

The claims of the present application have been amended to focus more particularly on microvascular blood volume magnetic resonance imaging. As disclosed in the present application:

> Reconstructed images acquired using inversion-recovery blood-nulling magnetic resonance sequences contain information pertaining to vascular space occupancy insofar as the images includes contributions from tissue but substantially exclude contributions from the blood volume. By applying a physiological perturbation, the blood volume can be changed. ... [T]he change in blood volume occurs principally in the microvessels rather than in the large vessels and parenchyma. Advantageously, the blood volume changes measured using the blood-nulled reconstructed images reflect the parenchymal blood volume (denoted BV herein) which substantially corresponds to the volume of the microvessels without contributions from the larger vessels. In contrast, vascular volume effects measured by BOLD and many other existing techniques include the large vessels and parenchyma and other tissues close to these vessels (for example, cerebral spinal fluid). For parenchymal tissue (tissue with perfused blood), the parenchymal vascular space occupancy (VASO, also denoted ξ herein) is given by:
>
> $$\xi = \frac{BV}{BV + V_{tissue}} = \frac{BV}{V_{par}} \quad (1)$$
>
> where BV is the blood volume, V_{tissue} is the pure tissue volume (without blood), and V_{par} is the volume of the parenchymal tissue, that is, $V_{par}=BV+V_{tissue}$. The measured parenchymal vascular space occupancy ξ advantageously is more sensitive to physiological perturbation, including permanent disease-induced

> perturbation, than is the total vascular volume. Changes in large-vessel volume (that is, outside parenchymal regions) are also accessible by the blood nulling approach. At appropriate resolution, changes in large-vessel volume do not interfere with the indicated parenchymal blood volume changes due to the applied spatial encoding.
>
> Present application at page 9 line 14-page 10 line 9.

The present application measures microvascular blood volume effects through signal changes in the parenchymal tissue signal. This effect can be detected by substantially reducing (e.g., nulling) the blood signal. The present application recognizes that acquiring a blood nulled or blood signal reduced signal amounts to acquiring a predominantly parenchymal tissue signal in which the blood signal is substantially reduced relative to the parenchymal tissue signal, and further recognizes that by applying a suitable perturbation to vary the parenchymal vascular space occupancy (VASO or ξ) one can assess the microvascular blood volume without reliance upon exogeneous contrast (e.g., using an administered magnetic contrast agent) and without reliance upon endogenous paramagnetic contrast (e.g. BOLD).

The Applied References

Song relates to the use of blood nulling for studying the extent of arterosclerotic lesions in the vascular wall of large vessels (macrovessels) such as carotid and coronary arteries. This is a "black blood" technique – by nulling the blood signal, the vascular walls of large vessels have improved image contrast, which facilitates detection of arterosclerotic lesions. Song does not relate to assessment of microvascular blood volume (that is, the parenchymal blood volume BV perfused in the parenchymal tissue), and does not recognize that the blood-nulled signal could be used for such assessment.

Other distinctions of the present application respective to Song as follows. First, Song's imaging of vessel walls requires imaging at high spatial resolution, while the imaging of microvascular blood volume changes disclosed in the present application does not. The novel microvascular blood volume assessment methods disclosed herein enable enhanced functional localization, both at high and at lower spatial resolution.

Second, the techniques of the present application can utilize a single non-selective radiofrequency (RF) inversion pulse (i.e. of sufficient excitation range) to null the blood. Song and the Edelman reference (Radiology, vol. 181, 655-660 (1991)) therein use two inversion pulses – a non-selective pulse followed by a slice-selective inversion pulse. The blood nulling approach of the present application is readily extended to keep nulling the blood with multiple inversion pulses, while the non-selective/selective inversion combination of Song and Edelman cannot.

Third, the Song and Edelman approaches require blood to flow into the slice to be imaged, while the spatially non-selective nulling of the present application does not.

The Office Action appears to recognize these deficiencies in Song, and relies upon Van Zijl to allegedly remedy these deficiencies.

Van Zijl relates to the blood oxygenation level dependent (BOLD) image contrast technique. BOLD entails measuring the blood signal and performing blood volume assessment using the blood signal. Van Zijl actually teaches away from the techniques claimed in the present application, since Van Zijl relies upon the (BOLD) blood signal whereas the techniques of the present application intentionally reduce or null the blood signal and instead utilize a predominantly parenchymal tissue signal to assess the microvascular blood volume.

More particular distinctions between the microvascular blood volume assessment approaches of the present application and the BOLD techniques of Van Zijl are as follows. First, the effects in van Zijl are based on the total signals of tissue and blood, while the approaches of the present application acquire and analyze the tissue signal alone, with the blood signal substantially suppressed.

Second, in Van Zijl the effects measured are paramagnetic (blood-oxygenation-level-dependent or BOLD) effects taking place predominantly in blood, while the techniques of the present application acquire and analyze signals that are not paramagnetic and are obtained from the tissue, not the blood. Contrary to Van Zijl, in the present application the signals of blood are substantially reduced or nulled, and are not used in the microvascular blood volume assessment.

Third, the signal acquired and analyzed by van Zijl is dependent on blood flow, blood volume and blood oxygenation (BOLD signal) while the techniques of the present application are sensitive to blood volume. This avoids errors due to confusion of other effects with changes in microvascular blood volume. For example, in van Zijl a signal reduction is observed with hypoxia due to the oxygenation change, not the blood volume change (see fourth point immediately below).

Fourth, in van Zijl an assumption is made that the water signal in the tissue does not change with blood volume changes. See Van Zijl page 162, righthand column. To the contrary, the techniques of the present application are based on the recognition that the water signal in the tissue does change with blood volume changes. Again, Van Zijl teaches away from the techniques of the present application.

The Claims Present Patentable Subject Matter and Should Be Allowed

Claim 1 as set forth herein calls for performing a blood signal-reduction magnetic resonance excitation sequence that substantially reduces a magnetic resonance signal from blood while substantially retaining parenchymal tissue signal; subsequently performing a readout magnetic resonance sequence to acquire a magnetic resonance signal arising predominantly from parenchymal tissue; and determining a microvascular blood volume parameter based on the acquired magnetic resonance signal arising predominantly from parenchymal tissue.

Song discloses a blood signal reduction sequence, in the form of a blood nulling sequence. However, Song uses blood nulling as a "black blood" technique to eliminate the blood signal so as to provide enhanced contrast for the inner vascular wall, for example to facilitate detection of arterosclerotic lesions. Song does not disclose or fairly suggest determining a microvascular blood volume parameter based on the acquired magnetic resonance signal arising predominantly from parenchymal tissue.

Van Zijl cannot remedy this deficiency of Song, at least because Van Zijl teaches that the magnetic resonance signal from parenchymal tissue does not change with changing blood volume. This teaches away from the recitation in claim 1 of determining a microvascular blood volume parameter based on the acquired magnetic resonance signal arising predominantly from parenchymal tissue. The skilled artisan reading Van

Zijl would conclude that the determination recited in claim 1 is not possible because the parenchymal tissue signal is (according to Van Zijl) independent of blood volume.

Claim 23 has been amended to incorporate the subject matter of canceled claims 27 and 28, and to focus more particularly on microvascular blood volume magnetic resonance imaging. Claim 23 calls for a magnetic resonance system configured to determine changes in microvascular blood volume without the use of exogenous contrast or endogenous paramagnetic contrast using the parenchymal tissue signal, the system including: a blood signal reduction means for performing a blood signal reduction magnetic resonance excitation sequence that substantially reduces a magnetic resonance signal from blood while retaining an effective parenchymal tissue signal; a readout means for performing a readout magnetic resonance sequence to acquire a magnetic resonance signal arising predominantly from parenchymal tissue, the readout means operating subsequent to operation of the blood signal reduction means; a reconstruction means for generating a reconstructed image from the acquired magnetic resonance signal; and a means for computing a blood volume parameter value from the reconstructed image.

Again, Song discloses blood nulling for performing black blood imaging to detect arterosclerotic lesions, but does not relate to computing a blood volume parameter.

Van Zijl relates to assessing blood volume, but employs a wholly different technique based on BOLD contrast. Far from making obvious the system of claim 23, Van Zijl to the contrary teaches that one cannot construct a system to compute a blood volume parameter value from an image reconstructed from a magnetic resonance signal arising predominantly from parenchymal tissue, because according to Van Zijl the magnetic resonance signal from parenchymal tissue does not vary with blood volume.

Claim 32 calls for a magnetic resonance method for assessing microvascular blood volume, the method comprising: acquiring a parenchymal tissue magnetic resonance signal from parenchymal tissue under different parenchymal blood volume perturbing conditions that change the vascular space occupancy within the parenchymal tissue; and determining a parenchymal vascular space occupancy-related parameter

based on the acquired parenchymal tissue magnetic resonance signals. This claim is supported in the original specification at least by Fig. 3 and related text.

Song acquires a parenchymal tissue magnetic resonance signal as part of its black blood imaging. However, Song does not remotely suggest the method for assessing microvascular blood volume as set forth in claim 32. The BOLD techniques of Van Zijl acquire a (BOLD) blood signal for assessing blood volume, and moreover Van Zijl teaches that a parenchymal tissue magnetic resonance signal does not change with blood volume (and hence is not probative of microvascular blood volume). Accordingly, Van Zijl cannot remedy the aforementioned deficiencies of Song.

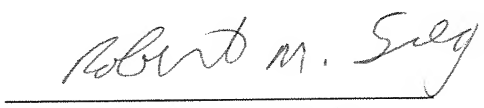
Each of the remaining claims depend directly or indirectly from one of claims 1, 23, or 32. For at least this reason, it is respectfully submitted that these dependent claims patentably distinguish over Song, Van Zijl, and their combination.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that claims 1-5, 12-16, 18-20, 22-24, and 29-34 (all claims) are in condition for allowance, and earnestly request reconsideration and allowance of claims 1-5, 12-16, 18-20, 22-24, and 29-34 (all claims).

Respectfully submitted,

FAY, SHARPE LLP



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